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Published
With international search report.

(54) Title: A METHOD OF TREATING A PATIENT WITH A BIOLOGICALLY ACTIVE COMPOUND

(57) Abstract

A method of preventing or reducing the formation of Factor VIII inhibitory antibodies in a patient suffering from Haemophilia A and not previously treated with Factor VIII or treated with a very limited amount of Factor VIII, the method comprising administration to the patient of a therapeutically effective amount of an immunoglobulin formulation before or during the initial treatments with Factor VIII.

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TITLE

A Method of Treating a Patient with a Biologically Active Compound.

FIELD OF THE INVENTION

The present invention relates to a method for treating a patient with an immunoglobulin formulation to prevent development of antibodies against Factor VIII in patients suffering from haemophilia A, and the use of an immunoglobulin formulation for the preparation of a pharmaceutical preparation for preventing inhibitor formation in patients suffering from haemophilia A when instituting treatment with Factor VIII.

BACKGROUND OF THE INVENTION

Haemophilia A is an X-chromosome-linked inherited disease which afflicts 1-2 males per 10,000. The disease is caused by an absence of deficiency of Factor VIII:C. Factor VIII:C is a very large glycoprotein (native M_r 330 K - 360 K), which is present in plasma at extremely low concentrations. It is a necessary element in the proteolytic cascade which converts soluble fibrinogen to insoluble fibrin, forming a clot to prevent blood loss from traumatized tissue. In the bloodstream, it is found in noncovalent association with von Willebrand factor (vWF) which acts as a stabilizing carrier protein. Factor VIII:C is very susceptible to cleavage by thrombin, Factor Xa, protein C, and other serine proteases. It is generally isolated from plasma or plasma products as a series of related polypeptides ranging from M_r 160 K-40 K with predominant species of M_r 92 K and M_r 80 K-77 K. This complex pattern has made the analysis of the structure of active Factor VIII:C very difficult.

The conventional treatment of haemophilia A is replacement therapy comprising administration of Factor VIII (antihaemophilic factor, or "AHF"). Such administration may be therapeutic to control an acute bleeding episode or prophylactic to prevent bleeding episodes in order to allow the patient to normalize his life.

Factor VIII:C and the related polypeptides have been described by F. Rotblat et al, Biochemistry (1985) 24:4294-4300; G.A. Vehar et al, Nature (1984) 312:337-342; J.J. Toole et al, Nature (1984) 312:342-347; and M.A. Truett et al, DNA (1985) 4:333-349. The sequence has been reported by J.J. Toole et al, supra; W.I. Wood et al, Nature (1984) 312:330-336; and M.A. Truett et al, supra.

The Factor VIII administered to haemophiliacs may be purified in various ways from the plasma of donors or produced by recombinant DNA techniques.

However, some haemophiliacs develop inhibitors to Factor VIII and therefore exhibit resistance to the treatment in that administration of Factor VIII in doses which are usually effective for most haemophiliacs produces reduced or no therapeutic effect. Inhibitors are antibodies against Factor VIII:C which develop in response to the Factor VIII treatment of previously untreated patients (PUPs). The antibodies specifically neutralize the Factor VIII procoagulant activity.

Patients with inhibitors pose serious treatment problems since they are resistant to ordinary Factor VIII replacement therapy.

Lusher et al, New England Journal of Medicine, Vol 328, No.7, pp 453-458, February 18,1993 discloses that treatment of PUPs with haemophilia A using recombinant Factor VIII gave rise to development of inhibitor antibodies to Factor VIII in 16 of 81 patients.

Hoyer, J.Lab.Clin. Med.1993;121:385-387 discloses that inhibitor patients constitute a continuing problem and that they may be treated using porcine Factor VIII or, in the

alternative, the inhibitor may be eliminated through immunosuppression. Cytotoxic drugs such as cyclophoshamide or prednisone were found to be effective in treatment of some Factor VIII autoantibody patients. Furthermore, i.v. immunoglobulin appeared to reduce the antibody titer in some autoantibody plasmas, but the reduction was rarely sufficient to permit effective Factor VIII therapy. Hoyer proposes to bypass Factor VIII using Factor VIIa, prothrombin complex concentrate or activated prothrombin complex concentrate.

Lusher et al, Pediat. Res., 33 (4), p 142A (1993), (Abstract) disclose that from about 18% to about 52% of PUPs develop inhibitor antibodies against both recombinant or plasma derived Factor VIII.

Peerlinck et al, Blood, Vol.81, No.12(June 15),1993;pp 3332-3335 found that development of neutralizing antibodies to infused Factor VIII remains a major problem and that PUPs treated with monoclonal antibody purified FVIII concentrates or recombinant FVIII concentrates seem to have a higher incidence of isoantibody formation than patients treated with less pure products.

The treatment of inhibitor patients is expensive as the inhibitory effect must be suppressed by administration of very large doses of Factor VIII before a therapeutic effect is achieved. In WO 86/02838 it has been proposed to suppress the inhibitory antibodies using a formulation comprising a protein or peptide having specific Factor VIII antigen activity, e.g. a fraction of the Factor VIII molecule having a molecular weight of 77/80 K, in order to "saturate" the antibodies before giving the therapeutic dose of Factor VIII. Such a condition creates a difficult therapeutic situation for the patient.

Nilsson et al., Thromb. Haemost. 70(1), 1993, pp 56-59, disclose that patients with Factor VIII inhibitors may be treated for temporary reduction of the inhibitors by extensive plasma exchange, controlled extracorporal protein A adsorption for removal of antibodies or specific immunoadsorption for removal of antibodies. An immune

tolerance may be obtained by removal of antibodies and treatment of patients with alloantibodies by high dosage regimen of Factor VIII, by low or intermediate dosage regimen or by combined treatment using cyclophosphamide and thereafter high doses of i.v. IgG.

Macik, Seminars in Thrombosis and Hemostasis, Vol. 19, No.1, 1993 discloses that infusion of large doses of i.v. IgG may block inhibitor effect in inhibitor patients. However, the treatment is not uniformly reliable for all patients and it may require years of treatment in order to achieve a sustained response.

Thus, it would be desirable to avoid the development of Factor VIII inhibitors, first of all for a therapeutic point of view, but also for economical reasons.

In WO 91/08773 it is disclosed that covalently bound conjugates of immunoglobulins and proteins such as an antigen may be used for inhibiting an immune response in a mammal to a protein such as Factor VIII. However, it is not desirable to create new sequences and conformations, not recognized as native by the patient, in pharmaceuticals to be given to a human being due to the risk of antigenicity.

DESCRIPTION OF THE INVENTION

In a first aspect, the present invention relates to a method of preventing or reducing the formation of Factor VIII inhibitory antibodies in a patient suffering from Haemophilia A and not previously treated with Factor VIII or only treated with a very limited amount of Factor VIII, the method comprising administration to the patient of a therapeutically effective amount of an immunoglobulin formulation before or during the initial treatments with Factor VIII.

In normal individuals, there seems to be an "equilibrium" between autoantibodies and anti-idiotypic antibodies reactive with these autoantibodies. If this equilibrium is permanently disturbed, an autoimmune disease develops. The equilibrium may,

however, be restored and the autoimmune disease will disappear. Thus, anti-idiotypic antibodies against Factor VIII autoantibodies have been found in remission sera of patients with a previous anti-Factor VIII autoimmune disease (Y. Sultan et al., Proc. Natl. Acad. Sci. USA 84, 1987, pp. 828-831).

The mechanism whereby intravenously administered immunoglobulin may influence the formation of inhibitory antibodies to Factor VIII in preveiously untreated patients (PUPs) remains to be elucidated. It is, however, likely that immunoglobulin preparations primarily act through variable region-mediated mechanisms by providing the patient with regulatory elements of the normal immune system, thus providing physiological antibody-dependent control of autoreactivity (cf. L. Mouthon et al., Vox Sang. 67, 1994, pp. 53-59).

In the present context, the term "very limited amount of Factor VIII" is intended to refer to the situation where newborn children have been treated with Factor VIII substantially immediately after birth to stop bleeding incurred during birth, but have not subsequently been subjected to regular Factor VIII treatment.

In an embodiment of the invention, the immunoglobulin formulation is a concentrate prepared from plasma obtained from normal donors, in particular a large number of normal donors. The immunoglobulin formulation primarily contains IgG although smaller amounts of other immunoglobulins such as IgM, IgA and IgE may also be present, or it may be mixture of immunoglobulins, such as a mixture of IgG and IgM.

In another aspect, the invention relates to the use of immunoglobulin for the preparation of a medicament for preventing or reducing the formation of Factor VIII inhibitory antibodies in a patient suffering from Haemophilia A and not previously treated with Factor VIII or treated with only a very small amount of Factor VIII.

In a further aspect, the invention relates to a pharmaceutical kit for preventing or reducing the formation of Factor VIII inhibitory antibodies during treatment with

Factor VIII of a patient suffering from Haemophilia A and not previously treated with Factor VIII or treated with only a very limited amount of Factor VIII, said kit comprising, in separate containers,

(a) a formulation comprising an immunoglobulin or a mixture of immunoglobulins and

(b) a formulation comprising Factor VIII.

The kit may also comprise measured amounts of a pharmaceutically acceptable vehicle, preferably sterile water for reconstituting the formulations.

The Factor VIII to be used in accordance with the present invention may be Factor VIII isolated from plasma by methods known per se, e.g. as described in EP patent No. 83483, EP patent No. 150735 or EP patent No. 197901 or produced by recombinant techniques, e.g. as described in the patent applications listed below.

The preparation of recombinant proteins having Factor VIII activity by recombinant techniques has inter alia been disclosed in a number of patent publications. Thus, European Patent Application No. 160 457 and International Patent Application No. WO 86/01961 disclose the production of full length Factor VIII:C, and European Patent Application No. EP 150 735, International Patent Application No. WO 86/06101, European Patent Application No. EP 232 112, International Patent Application No. WO 87/04187, International Patent Application No. WO 87/ 07144, International Patent Application No. WO 88/00381, European Patent Application No. EP 251 843, European Patent Application No. EP 253 455, European Patent Application No. EP 254 076, U.S. Patent No. 4.980.456, European Patent Application No. EP 294 910, European Patent Application No. EP 265 778, European Patent Application No. EP 303 540, International Patent Application No. WO 91/07490, and International Patent Application No. WO 91/09122 disclose recombinant expression of Factor VIII having one or more deletions in the molecule, subunits of Factor VIII or co-expression of subunits for the production of complexes showing coagulant activity or binding affinity to antibodies inhibiting Factor VIII.

Pharmaceutical formulations comprising an immunoglobulin or a mixture of immunoglobulins may be any conventional immunoglobulin formulation in solution or in a lyophilized state comprising immunoglobulins and conventional additives and excipients such as saccharides or sugar alcohols, salts and stabilizers. Lyophilized formulations are reconstituted before administration, e.g. in sterile water. The immunoglobulin may be given by subcutaneous or intramuscular injection or by intravenous infusion. The dose of immunoglobulin may vary from about 0.1 to about 5 g per kg body weight per day. A preferred dose regimen in accordance with the present invention is about 1 g/kg/day administered by i.v. infusion before the administration of Factor VIII and continuing once a week for from 1 to 14 weeks, preferably for 12 weeks. The immunoglobulin treatment may be repeated one or more times by administration of booster doses, for example after 18 and 24 weeks. The immunoglobulin formulation may e.g. be the preparation commercially available from Novo Nordisk A/S, Bagsvaerd, Denmark under the trade mark Nordimmun®.

Pharmaceutical formulations comprising Factor VIII may be any conventional formulation in a lyophilized state comprising Factor VIII and conventional additives and excipients such as saccharides or sugar alcohols, salts and stabilizers for reconstitution before administration, e.g. using sterile water. The therapeutic dose level of Factor VIII may vary from about 100 IU to about 2000 IU given by i.v. infusion being decided by the physician supervising the administration in accordance with the individual patient's need. A prophylactic treatment may e.g. comprise giving from about 25 IU Factor VIII per kg bodyweight every other day up to about 200-300 IU Factor VIII per kg bodyweight per day. A preferred does regimen is from 10 to 50 IU/kg body weight three times weekly, although higher or more frequent doses are sometimes appropriate, especially in the treatment of younger children. The Factor VIII formulation may e.g. be the preparation commercially available from Novo Nordisk A/S, Bagsvaerd, Denmark under the Trade Mark Nordiocto® or Nordiate® or preparations available from e.g. Miles Inc. or Baxter Biotech or Armour Pharmaceutical Company under the Trade Marks Kogenate® or Recombinate® or Monoclate®.

The invention is explained more in detail in the below Example which illustrates the invention. It is not to be considered as limiting the scope of the invention being defined by the appended claims.

MATERIALS AND METHODS

Nordimmun® (i.v.)-preparation

Nordimmun® (i.v.) injection formulation from Novo Nordisk A/S, Plasma Product Unit contains human immunoglobulin G manufactured from plasma representing a donor pool per batch of more than 2,000 healthy, adult volunteers.

Nordimmun® 5 g i.v. injection formulation contains 5.0 g freeze-dried human immunoglobulin G. The reconstituted product contains 4.6% human immunoglobulin G, 1.5% human albumin, 4.6% sucrose, and max 0.15 M sodium.

Factor VIII-preparation

The Factor VIII preparation is an injection formulation containing Factor VIII purified directly from plasma. The Factor VIII preparation has a high degree of purity and a specific activity > 100 IU/mg protein prior to formulation with albumin. The preparation is virus-inactivated by two different methods, the so-called solvent-detergent (S/D) method and dry-heat treatment at 80°C for 72 hours.

The Factor VIII injection formulation is manufactured as 250 IU, 500 IU, and 1000 IU vials to be dissolved in sterile volume in a volume of 5 ml, 5 ml, and 10 ml, respectively.

EXPERIMENTAL PART

A double blind study is set up to see whether inhibitor formation in patients may be prevented through preventive treatment combining Factor VIII and immunoglobulin therapy in the initial phase.

Patients in the Study

The trial includes patients who have previously had no more than 2 treatments with FVIII for their haemophilila A (PUPs).

Inclusion criteria (all criteria have to be fulfiled)

1. Severe or moderate haemophilia A.
2. Not had more than 2 treatments with Factor VIII preparations.
3. Written informed consent of the parents or legal guardian before undertaking of any study procedures.

Exclusion Criteria

1. Patients with a known lack of IgA.
2. Participation in another study.
3. Patients with known or suspected allergy to trial products or related products.

Examinations at hospital prior to treatment with Nordimmun® injection substance/Placebo

At inclusion in the study the patient is allocated a study number, and the patient initials as well as demographic data are written in the Case Record Forms.

Before inclusion in the study a clinical examination of the patient will be carried out. The clinical examination will be repeated at the concluding control visit of the study.

The following laboratory parameters are taken at inclusion and with regular intervals until the end of this study.

* Antibodies against Factor VIII (inhibitor).
* ALT (alanine aminotransferase)
* Bilirubin.
* Haematocrit (erythrocyte volume)
* Haemoglobin.
* Leucocytes and differential count.
* Thrombocytes.
* Coagulation factor II-VII-X
* Virological markers (HBsAg, anti-HBs IgG and IgM, Anti-HCV, anti HIV 1 + 2, and anti-Parvo B19 IgG and IgM.
* IgG, IgA, IgM.

After enrolment in the study all pateints will attend treatment on an outpatient basis, according to the flow chart.

The follow-up period starts after week 8.

Over a period of at least 6 months all patients are routinely tested to see if formation of antibodies against the Factor VIII preparation occurs.

Weeks 12 and 24, at the concluding control visit, blood sampling and a clinical examination - similar to the one at study entry - is carried out.

The presence of Factor VIII inhibitors is the parameter for evaluation of efficacy between treatment groups.

Prior to start of the study and with regular intervals until the end of the study, blood samples are taken to examine whether formation of antibodies against Factor VIII occurs.

Virological markers, HBsAg, anti-HBs IgG and IgM, anti-HCV, anti-HIV 1 + 2, and anti-Parvo virus IgG and IgM are tested for in blood samples prior to start of the study and at regular intervals until the end of study.

It is a well-known fact that some haemophiliacs are likely to be seropositive to one or more of the mentioned virological tests, due to either vaccination or infection with the corresponding virus. Treatment with immunoglobulins will lead to positive tests for anti-HBs IgG and anti-Parvo IgG, these antibodies being vontained in the immunoglobulin preparations.

Consequently, the extent to which the virological parameters will serve the purpose of evaluation of the safety parameters will be individual.

Flow chart

	Inclusion	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 24
Inclusion/Exclusion criteria	x							
IgG, IgA, IgM	x							x
Written, informed consent	x							
Clinial Examination *	x							x
Concomitant illness	x	x	x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x	x
Recovery *	x						x	x
IgG infusion	x	x	x	x	x	x	x	
Erythrocyte volfr.(hematocrit) HgB, leucocytes	x	x	x	x	x	x	x	x
Differential count thrombocytes	x	x	x	x	x	x	x	x
Factor II, VII, C	x	x	x	x	x	x	x	x
ALAT	x	x	x	x	x	x	x	x
Bilirubin	x	x	x	x	x	x	x	x
Antibodies against Factor VIII (inhibitor) *	x						x	x
Virology **	x	x	x	x	x	x	x	x
Registration of adverse events		x	x	x	x	x	x	x

* If the patient withdraws, also at the time of withdrawal

** HBsAg, anti-HBs IgG+IgM, Anti-HCV, Anti-HIV I + II, and anti-Parvo B.19 IgG+IgM (to be frozen)

Nordimmun® infusion is given ≥ 1 hour prior to the FVIII infusions.

Factor VIII therapy is on a three days a week prophylactic treatment regimen through the 6 months period.

CLAIMS

1. A method of preventing or reducing the formation of Factor VIII inhibitory antibodies in a patient suffering from Haemophilia A and not previously treated with Factor VIII or only treated with a very limited amount of Factor VIII, the method comprising administration to the mammal of a therapeutically effective amount of an immunoglobulin formulation before or during the initial treatments with Factor VIII.

2. A method as claimed in claim 1 wherein the immunoglobulin formulation is a concentrate prepared from plasma obtained from normal donors.

3. A method as claimed in claim 2, wherein the immunoglobulin formulation is a concentrate prepared from plasma obtained from a large number of normal donors.

4. A method as claimed in claim 2, wherein the immunoglobulin formulation comprises a mixture of immunoglobulins.

5. A method as claimed in any of claims 1-3, wherein the immunoglobulin formulation is an IgG formulation.

6. A method as claimed in any of claims 1-5, wherein the immunoglobulin formulation is administered in a dose of from about 0.1 g to about 5 g per kg body weight per day, in particular about 1 g/kg body weight/day.

7. A method as claimed in claim 6, wherein the immunoglobulin formulation is administered once a week for 1-14 weeks, preferably for 12 weeks.

8. Use of immunoglobulin for the preparation of a medicament for preventing or reducing the formation of Factor VIII inhibitory antibodies in a patient suffering from

Haemophilia A and not previously treated with Factor VIII or only treated with a very limited amount of Factor VIII.

9. Use as claimed in claim 8, wherein the immunoglobulin formulation is a concentrate prepared from plasma obtained from normal donors.

10. Use as claimed in claim 9, wherein the immunoglobulin formulation is a concentrate prepared from plasma obtained from a large number of normal donors.

11. Use as claimed in claim 9, wherein the immunoglobulin formulation comprises a mixture of immunoglobulins.

12. Use as claimed in claim 8, wherein the immunoglobulin is IgG.

13. Use as claimed in any of claims 8-12, wherein the immunoglobulin is present in amount sufficient to provide a daily dose of from about 0.1 g to about 5 g per kg body weight, in particular about 1 g/kg body weight.

14. A pharmaceutical kit for preventing or reducing the formation of Factor VIII inhibitory antibodies during treatment with Factor VIII of a patient suffering from Haemophilia A and not previously treated with Factor VIII or only treated with a very limited amount of Factor VIII, said kit comprising, in separate containers,

(a) a formulation comprising an immunoglobulin or a mixture of immunoglobulins and

(b) a formulation comprising Factor VIII.

15. A kit as claimed in claim 14, wherein the immunoglobulin formulation is a concentrate prepared from plasma obtained from normal donors.

16. A kit as claimed in claim 15, wherein the immunoglobulin formulation is a concentrate prepared from plasma obtained from a large number of normal donors.

17. A kit as claimed in claim 14, wherein the immunoglobulin formulation is an IgG formulation.

18. A kit as claimed in claim 14, wherein the immunoglobulin formulation contains immunoglobulin in an amount providing a daily dose of from about 0.1 g to about 5 g per kg body weight, in particular about 1 g/kg body weight.

19. A kit as claimed in claim 14, wherein the Factor VIII formulation contains Factor VIII in an amount of from about 100 IU to about 2000 IU.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 95/00330

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 39/395, C07K 16/36 // C07K 16/42
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, EMBASE, SCISEARCH, WPI, WPIL, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Dialog Information Services, file 155, Medline, Dialog accession no. 09096049, Medline accession no. 95026049, Sultan Y et al: "The use of intravenous immunoglobulins in the treatment of factor VIII inhibitors", & Semin Hematol (UNITED STATES) Apr 1994, 31 (2 Suppl 4) p65-6 --	8-19
X	Dialog Information Services, file 73, Embase, Dialog accession no, 9091587, Embase accession no. 94027273, Struillou L.: "Acquired hemophilia in a patient with rheumatoid arthritis. Beneficial effect of intravenous immune globulin", & REV. RHUM. ENGL. ED. (France), 1993, 60/7-8 (434-436) --	8-19

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
22 November 1995	28 - 11 - 1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Palmcrantz Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Dialog Information Services, file 155, Medline, Dialog accession no. 05334014, Medline accession no. 84258014, Gianella-Borradori A: "Haemophilia due to factor VIII inhibitors in a patient suffering from an autoimmune disease: treatment with intravenous immunoglobulin. A case report", & Blut (GERMANY, WEST) Jun 1984, 48 (6) p403-7 --	8-19
X	Dialog Information Services, file 155, Medline, Dialog accession no. 07894476, Medline accession no.92032476, Sultan Y: "Treatment of factor VIII inhibitors", & Blood Coagul fibrinolysis (ENGLAND) Jun 1990, 1 (2) p193-9 --	8-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 95/00330

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-7
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by therapy.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.